Observational Study

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Multidisciplinary treatment of advanced or metastatic ALK-positive non-small cell lung cancer

Real-world data on Brigatinib combined with local therapy

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Abstract

Anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) often shows incomplete responses and progression despite tyrosine kinase inhibitor (TKI) therapy. Preliminary data suggest that combining brigatinib, an ALK-selective TKI, with surgery or radiotherapy may improve outcomes. We retrospectively analyzed patients with advanced ALK-positive NSCLC who received brigatinib as first-line treatment combined with local therapy to assess safety and efficacy of this approach in a real-world setting. Among 9 patients, 6 (67%) had stage III and 3 (33%) had stage IV adenocarcinoma. Five patients received surgery, 3 received radiotherapy, and 1 received both. Brigatinib-related adverse events (AEs) occurred in 78% of patients, primarily mild (grade ≤ 2). Severe AEs (grade ≥ 3) were seen in 22% of patients and included dyspnea and hypertension. Brigatinib was discontinued in 22% of patients due to toxicity. Local therapy-related AEs were mostly grade 1. The objective response rate was 89%, with 2 complete and 6 partial responses. At data cutoff, brigatinib was ongoing in 55% of patients, with a median treatment duration of 14 months and a 2-year progression-free survival rate of 100%. Combining brigatinib with local therapy appears safe and potentially more effective for advanced ALK-positive NSCLC. Further studies are warranted.

Abbreviations: AE = adverse event, ALK = anaplastic lymphoma kinase, CI = confidence interval, CR = complete response, CTCAE = common terminology criteria for adverse events, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, NGS = next-generation sequencing, NSCLC = non-small cell lung cancer, ORR = objective response rate, OS = overall survival, PD = progressive disease, PD-L1 = programmed death-ligand 1, PFS = progression-free survival, PR = partial response, RECIST = response evaluation criteria in solid tumors, SD = stable disease, TKI = tyrosine kinase inhibitor, TPS = tumor proportion score, VATS = video-assisted thoracoscopic surgery.

Keywords: ALK, brigatinib, local therapy, non-small cell lung cancer, radiotherapy, real-world evidence, surgery

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This analysis was reviewed and approved by the ethics committee of the city of Vienna, Austria (EK-20-061-VK).

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1. Introduction

Lung cancer has the highest incidence rate and number of cancer-related deaths worldwide.[1] The emergence of novel targeted therapies and immune checkpoint inhibitors has transformed the therapy landscape and improved outcomes for lung cancer patients.[2] Non-small cell lung cancer (NSCLC) patients with distinct driver mutations have particularly benefitted from recent advances.[3] Approximately 3% of NSCLC patients harbor EML4-anaplastic lymphoma kinase (ALK) rearrangements, which can be targeted using ALK-directed tyrosine kinase inhibitors (TKIs).[4] The rearrangement of ALK leads to its aberrant expression and activation of several signaling pathways that modulate tumor cell proliferation and survival.[5] The first-generation ALK-TKI, crizotinib, was granted FDA approval in 2011 and showed superiority in improving progression-free survival (PFS) compared to chemotherapy.[6] Currently, the standard of care for ALK-positive NSCLC includes next-generation ALK-TKIs such as alectinib, brigatinib, or lorlatinib, which offer significantly improved systemic and intracerebral efficacy compared to crizotinib.[4,7–10] However, 95% of patients who initially respond to ALK inhibition have residual disease and subsequently develop TKI-resistant cells.[11]

The BRIGHTSTAR trial (NCT03707938) is currently investigating the safety and efficacy of brigatinib in combination with local consolidative therapy.[12] The preliminary data of this study supports the rationale for investigating the combination of local therapies, such as surgery and radiotherapy, with ALK inhibition to determine whether these approaches are more effective in reducing residual disease and preventing tumor relapse. Targeting resistant tumor cells that escape systemic therapy, these combined modalities may offer a strategy to improve long-term disease control in patients with ALK-positive cancers.

In this study, we reviewed the safety and efficacy profile of combined local therapy (surgery, radiotherapy, or both) and brigatinib in advanced or metastatic ALK-positive NSCLC patients in a real-world setting.

2. Materials and methods

2.1. Study design

This descriptive, retrospective, single-center analysis aimed to assess the safety and efficacy of brigatinib in combination with surgical resection and/or radiotherapy in patients with stage III or IV ALK-positive NSCLC.

Digital health records from patients receiving combinatorial treatment between January 2022 and January 2024 at the Department of Thoracic Surgery and the Department of Respiratory and Critical Care Medicine at Clinic Floridsdorf in Vienna, Austria, were evaluated. This analysis was reviewed and approved by the Ethics Committee of the City of Vienna (EK-20-061-VK), Austria, and conducted in accordance with the Declaration of Helsinki.[13] All patients provided written informed consent for the analysis of their cancer-related medical data.

2.2. Patients

Patients were included if they met the following criteria: age ≥ 18 years, histopathological confirmation of lung adenocarcinoma, molecular pathological confirmation of EML4-ALK rearrangement, and were TKI-naïve or receiving first-line brigatinib at treatment start. Lung adenocarcinoma was confirmed histopathologically according to the 2015 WHO classification of Lung Tumors.[14] Tumor staging was performed according to the eighth edition of the lung cancer stage classification.[15] Next-generation sequencing (NGS) analysis of tumor tissue validated the presence of EML4-ALK rearrangements and corresponding variants. All patients received brigatinib as first-line systemic treatment in combination with local therapy such as surgery, radiotherapy, or both. Patients began brigatinib treatment with a starting dose of 90 mg QD for 1 week, then escalated to 180 mg QD. Dose reductions, interruptions, and drug withdrawals were decided at the treating physician's discretion. Brigatinib was discontinued due to disease progression or unacceptable toxicity.

2.3. Histopathological analysis

Histopathological profiling and molecular testing were performed at the Department of Pathology and Bacteriology at Clinic Floridsdorf. Histopathological samples were evaluated by a board-certified pathologist. Lung adenocarcinoma was determined based on histomorphological features or immunohistochemical positivity for TTF-1 according to the 5th edition of the WHO Classification of thoracic tumors.[16] ALK-Immunohistochemistry (VENTANA anti-ALK (D5F3) Assay) and Genomic profiling using NGS examined the presence of ALK Fusions and corresponding variants. For NGS analysis, DNA and RNA were extracted from formalin-fixed paraffin-embedded tissue using the MagMAX™ FFPE total nucleic acid isolation kit (thermo Fisher scientific). NGS was performed using the Ion Torrent Oncomine™ Focus Assay and the Ion GeneStudio™ S5 plus system (thermo Fisher scientific). In some cases, EML4-ALK rearrangements were detected using the Idylla™ GeneFusion Assay (Biocartis). PD-L1 expression was determined by immunohistochemistry (Ventana, Clone SP263, Roche Diagnostics) and the tumor proportion score (TPS) of PD-L1 was evaluated. The TPS is defined as the relative number of all tumor cells with partial and complete PD-L1 staining to all viable tumor cells.

2.4. Description of safety and efficacy

Objective response rates (ORR) were used to determine efficacy. Radiological response was routinely evaluated via CT every 2 to 3 months and according to the Response Evaluation Criteria in Solid Tumors version 1.1 criteria (investigator assessed), defined as partial response (PR), complete response (CR), stable disease, or progressive disease (PD). Imaging of the brain was done only in the presence of known or suspected brain metastases. Severity of adverse events (AEs) was evaluated by the treating physician and graded according to the National Cancer Institute's Common Terminology Criteria for AEs, version 5.

3. Results

3.1. Patient and treatment characteristics

Nine patients were included. The mean age of patients was 61 years (±11; range, 42–79), with 5 patients (56%) being male and 4 patients (44%) being never smokers (Table 1). All patients were diagnosed with adenocarcinoma, with 6 patients classified as stage III (67%) and 3 as stage IV (33%). ALK-immunohistochemistry was positive in all tested patients (n = 8) (Fig. 1). NGS analysis revealed that 5 patients (56%) harbored the EML4-ALK fusion variant 1, 3 patients (33%) had variant 3a/b, and 1 patient's variant was unknown. No relevant co-mutations were detected by local NGS. Stage IV patients presented with metastases to distant lymph nodes, bones, or the brain. Of these 3 patients, 2 had more than 3 metastases.

Comorbidities were present in 6 patients (67%), with hypertension being the most common, affecting 3 patients. Additionally, hyperthyroidism, hyperuricemia, severe kidney disease, congestive heart failure, fibromyalgia, hyperlipidemia, Hashimoto thyroiditis, and major depression were each observed in 1 patient. Six patients (67%) underwent surgery

Table 1

Patient and tumor characteristics.

Characteristics at diagnosis	All patients
Age, yr	
Mean (SD)	61 (±11)
Age groups, n (%)	
<65	6 (67%)
≥65	3 (33%)
Sex, n (%)	
Male	5 (56%)
Female	4 (44%)
Race, n (%)	
Asian	0 (0%)
Non-Asian	9 (100%)
ECOG performance status, n (%)	
ECOG 0	9 (100%)
Smoking status, n (%)	
Never smoker	4 (44%)
Former smoker	3 (33%)
Current smoker	2 (22%)
Pack years, n (%)	
Smoker (1–30py)	3 (33%)
Heavy smoker (≥ 30py)	2 (22%)
Stage at brigatinib initiation, n (%)	
Stage III	6 (67%)
Stage IIIa	3 (33%)
Stage IIIb	2 (22%)
Stage IIIc	1 (11%)
Stage IV	3 (33%)
Stage IVa	1 (11%)
Stage IVb	2 (11%)
Histological subtype, n (%)	
Adenocarcinoma	9 (100%)
EML4-ALK variants, n (%)	
variant 1	5 (56%)
variant 3a/b	3 (33%)
unknown	1 (11%)
PD-L1 status, n (%)	
Negative (<1%)	2 (22%)
1% to 49 %	4 (44%)
≥50 %	2 (22%)
Unknown	1 (11%)
Metastasis, n (%)	
Number of metastases at baseline	
≤3	7 (78%)
>3	2 (22%)
Location of metastasis	
Distant lymph node	2 (22%)
Bone	1 (11%)
Brain	1 (11%)

ALK = anaplastic lymphoma kinase, ECOG = Eastern Cooperative Oncology Group, PD-L1 = programmed death-ligand 1.

additional to brigatinib therapy (Fig. 2). Five patients who underwent surgery received video-assisted thoracic surgery lobectomy or bilobectomy, while 1 patient underwent lobectomy via thoracotomy. Lymphadenectomy was performed in all patients who underwent surgery. Four patients (44%) received brigatinib solely as adjuvant therapy and 2 patients (22%) in a perioperative (neoadjuvant plus adjuvant) setting. Brigatinib was initiated before radiotherapy only or initiated before and continued after radiotherapy (Fig. 2). Consolidating radiotherapy of lung and lymph node was administered at 24 Gy and 51 Gy, respectively. One patient (11%) received both radiotherapy and surgery, consisting of conformal radiotherapy of lung, bone and lymph node at 39 Gy and surgical resection of bone metastasis. In summary, brigatinib was initiated in 4 patients (44%) before and in 4 patients (44%) after ablative therapy, while 1 patient (11%) received it after surgery but before radiotherapy.

3.2. Safety

All patients received brigatinib as first systemic anticancer treatment. The median duration of brigatinib treatment was 14 months with a minimum of 2 and a maximum of 26 months. Brigatinib had to be discontinued in 3 patients (33%) due to toxicity and in 1 patient (11%) due to disease progression (Table 2). At the cutoff date, 5 patients (55%) patients were still receiving treatment with brigatinib.

Under brigatinib therapy, 7 patients (78%) exhibited adverse events (AEs). Five patients (44%) experienced low grade (≤grade 2) AEs including pain, weakness, thoracic pain, polyneuropathy, flatulence, elevated liver parameters and pneumonitis, while 2 patients (22%) experienced grade ≥ 3 AEs including hypertension (grade 3), dyspnea (grade 3) and blood pressure fluctuations (grade 4) (Table 2). Due to these toxicities, brigatinib dose was reduced in 3 patients (33%) from 180 mg to 90 mg and interrupted in 2 patients (22%) for 19 and 28 days, respectively. As mentioned, 3 patients (33%) had to discontinue treatment with brigatinib due to toxicity resulting in blood pressure fluctuations, pneumonitis and polyneuropathy.

One patient (11%), who started brigatinib therapy before surgery, had an interruption of 62 days. Two patients (22%) received radiotherapy additional to brigatinib, in these cases brigatinib therapy was initiated before radiotherapy and interrupted for 4 and 17 days, respectively. During local therapy, 3 patients receiving surgery and 1 patient receiving radiotherapy experienced AEs. All 3 patients (33%) who underwent surgery experienced grade 1 AEs including heart palpitations, shortness of breath and sore throat, while 1 patient (11%) who received radiotherapy experienced grade 2 AEs consisting of dysphagia, thrush esophagitis and whole-body pain. All patients successfully completed planned local treatment. The follow-up was between 8 and 28 months.

3.3. Efficacy

The ORR was 89%. CR and PR were reported in 2 (22%) and 6 (67%) patients, respectively (Table 3). However, in 1 patient the radiologic response was not evaluable (no target lesion). One patient had brain metastases, which showed a PR without intracranial local therapy. Images of the brain metastases before and after brigatinib therapy are shown in Figure 3. After 1 and 2 years, no patient showed evidence of PD (2-year PFS 100%). Tumor tissue of patients receiving brigatinib in a neoadjuvant setting, was histopathologically evaluated pre- and postoperatively, which revealed grade IIa therapy-induced tumor regression. Moreover, tumors regressed from T2a and T3 to yT1c and yT1b, respectively. One patient has progressed after 26 months of treatment. To this date, all patients are alive.

For the comparative analysis, we included an additional retrospective cohort consisting of all patients treated at our center who received brigatinib as first-line therapy without local treatment, totaling 9 patients. This analysis revealed a lower 1-year and 2-year PFS (67% and 53%, respectively). The ORR in this cohort was 89%, with 8 patients responding to treatment and 1 patient classified as a nonresponder. Further details on this retrospective comparison can be found in the supplementary materials (Table S1, Supplemental Digital Content, https://links.lww.com/MD/O766).

4. Discussion

Rearrangements of EML4-ALK occur in approximately 3% to 5% of NSCLC patients.[4] Recent clinical trials indicate that combining TKIs with local therapies could improve outcomes of NSCLC patients.[17–19] Currently, the BRIGHTSTAR (NCT03707938) trial investigates the safety and efficacy of

brigatinib in combination with local consolidative therapy.[20] Retrospective analysis of ORRs of the BRIGHTSTAR trial and the ALTA-1L (NCT02737501) revealed favorable PFS of patients treated with brigatinib and local consolidative therapy.[4,20] The 2-year PFS rate for brigatinib combined with local consolidative therapy was 80% compared to brigatinib-treated patients from the ALTA-1L study which showed a 2-year PFS of 56%.[4,12,20]

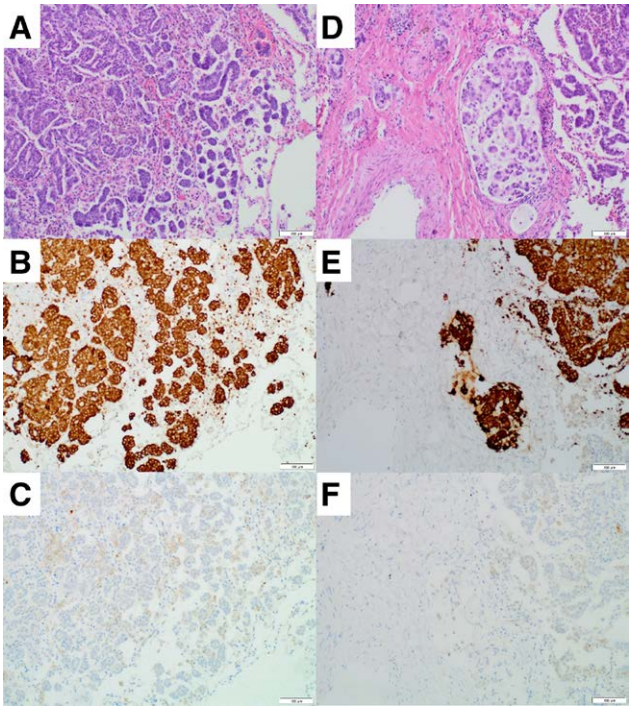

Figure 1. Invasive non-mucinous adenocarcinoma of the lung (Objective × 10, HE, immunohistochemistry) with STAS (A–C) and lymphangioinvasion (D–F). Strong granular cytoplasmic staining of the tumor with antibody against ALK (D5F3) and weak membrane staining in < 1% of tumor cells with antibody against PD-L1 (SP263). The bar indicates 100 µm. ALK = anaplastic lymphoma kinase, PD-L1 = programmed death-ligand 1.

Here, we present real-world data of 9 patients with advanced or metastatic NSCLC, who were treated with brigatinib and local therapy such as surgery and/or radiotherapy between January 2022 and January 2024. All patients underwent NGS-testing, which confirmed ALK-positivity. We observed an acceptable safety profile of brigatinib, with the majority of AEs being of low severity. Moreover, AEs in relation to local therapy occurred in 4/9 patients but were primarily graded 1. In addition, this multidisciplinary approach resulted in favorable ORR as 89% of patients exhibited partial or CRs during the treatment period, which was similar to the ORR of 79% as previously reported from the BRIGHTSTAR trial.[12] One patient with brain metastases showed PR without intracranial local treatment.

In line with our results, previous trials have reported a favorable safety profiles of brigatinib.[4,10] The most frequently reported AEs (≤grade 2) included diarrhea (38%–49%), elevated blood creatinine kinase levels (30%–39%), nausea (26%–40%), cough (25%–34%), and hypertension (21%–23%). Grade ≥ 3 AEs were seen in 61% of patients, with elevated blood creatinine kinase levels (9%–16%), hypertension (9%–10%), and increased lipase levels (13%) being the most common severe toxicities.[4,10] Consistent with these data, we present a similar safety profile and reported mostly low grade AEs of brigatinib, which likewise included musculoskeletal events (muscle pain, polyneuropathy), vascular disorders (hypertonia, blood pressure fluctuations) and gastrointestinal disorders (flatulence, elevated liver parameters). Dose-reduction rates of brigatinib (33%) were similar to previously reported trials.[4] Interestingly, early on-set pulmonary events (pneumonitis, interstitial lung disease) were more frequently observed in brigatinib-treated patients compared to crizotinib.[4,10] In our study 1 patient developed pneumonitis (grade 2) within 2 months of brigatinib initiation while 1

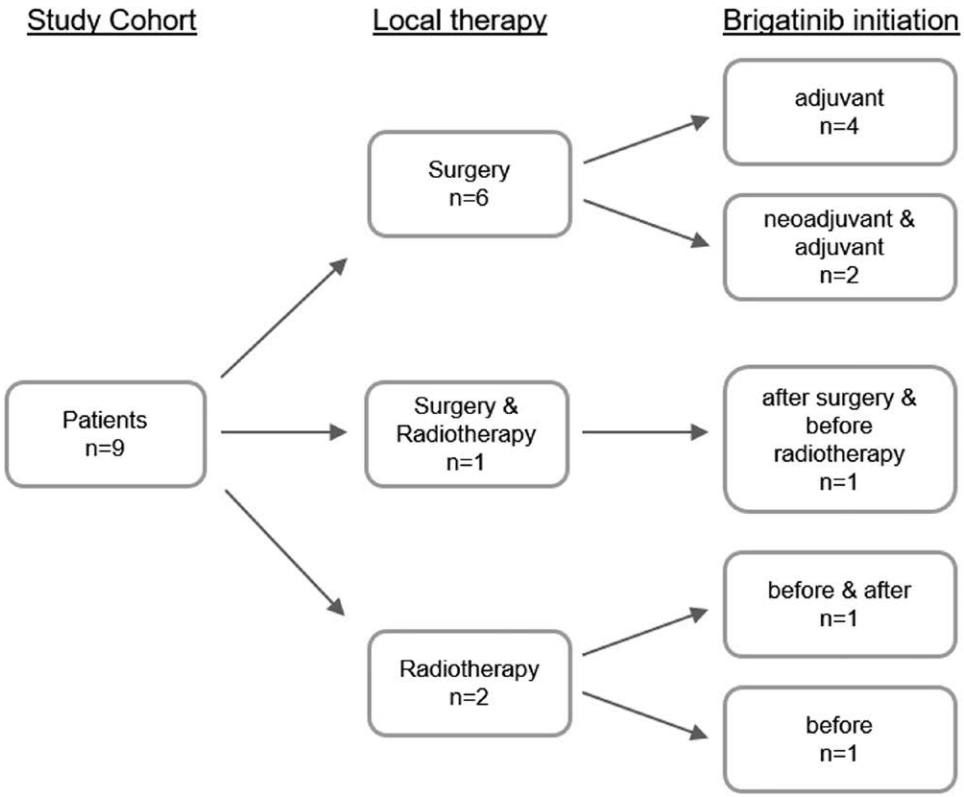

Figure 2. Treatment scheme. Flowchart depicts the treatment of enrolled patients with brigatinib and local therapy.

Table 2

Safety.

Patients (n = 9), n (%)							
AE under brigatinib	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Interruption**	**Dose reduction**	**Discontinuation**
	5 (55)	**5 (55)**	**2 (22)**	**1 (11)**	**2 (22)**	**3 (33)**	**3 (33)**
Musculoskeletal pain (thoracic pain, polyneuropathy)	3 (33)	1 (11)	0 (0)	0 (0)	1 (11)	2 (22)	
Weakness	0 (0)	1 (11)	0 (0)	0 (0)	1 (11)	1 (11)	
Hypertension	0 (0)	0 (0)	1 (11)	0 (0)	1 (11)	1 (11)	
Bood pressure fluctuations	0 (0)	0 (0)	0 (0)	1 (11)			1 (11)
Dyspnea	0 (0)	0 (0)	1 (11)	0 (0)			
Pneumonitis		1 (11)					1 (11)
Elevated liver parameters	1 (11)	2 (22)	0 (0)	0 (0)		1 (11)	
Flatulence	1 (11)	0 (0)	0 (0)	0 (0)			

Table 3

Efficacy.

Best radiologic response, n (%)	
Complete response	2 (22%)
Partial response	6 (67%)
Stable disease	0 (0%)
Progressive disease	0 (0%)
Not evaluable	1 (11%)
Progression-free survival rate (%)	
1-yr (n = 8)	100%
2-yr (n = 2)	100%

experienced dyspnea (grade 3) within 4 months. However, these AEs did not occur in the previously defined early on-set period of 14 days within brigatinib initiation and were not related to local therapy (both patients had surgery). AEs in relation to local therapy occurred in 4 patients (44%) and were graded ≤ 2, which is similar to patients receiving brigatinib and local consolidative therapy preliminary reported in the BRIGHTSTAR study.[20]

In our study, patients treated with brigatinib in combination with local therapies demonstrated a promising ORR and a 2-year PFS rate of 100%, suggesting that this approach may enhance patient outcomes. Notably, only 2 patients in our dataset received brigatinib for more than 2 years. When comparing these results to an additional retrospective cohort – consisting of 9 patients at our center who received brigatinib as first-line treatment without local therapy – we observed no difference in ORR but a lower 1-year and 2-year PFS (67% and 53%, respectively). While the small sample size limits definitive conclusions, these findings may suggest a potential benefit of local therapy in managing residual disease. However, it should also be taken into account that patients in the comparator group more frequently had stage IV disease (Table S1, Supplemental Digital Content, https://links.lww.com/MD/O766). At the cutoff date, all patients who received brigatinib in combination with radiotherapy are still receiving brigatinib and achieved either partial or CR. Recent studies have demonstrated that combining local therapy, such as surgery and radiotherapy with targeted therapy prolongs disease-free survival.[17,18,21] For example, patients with EGFR-mutant NSCLC benefit from receiving osimertinib in combination with radiotherapy or surgical resection.[18,21] In combination with surgery, neoadjuvant TKI treatment could induce tumor shrinkage, while adjuvant treatment may reduce the occurrence of residual disease, ultimately improving patient outcomes. The NeoADAURA trial (NCT04351555) currently examines the impact of neoadjuvant Osimertinib on pathological response and event-free survival in EGFR-mutant NSCLC patients.[22] In the ADAURA trial (NCT02511106) patients receiving adjuvant osimertinib exhibited improved survival compared to the placebo receiving group.[18] In patients with ALK-positive resected NSCLC, adjuvant alectinib has improved disease-free survival compared to adjuvant chemotherapy, further indicating the strength of this multimodal approach.[17] Combining TKIs with radiotherapy and surgery has already yielded success in improving ORRs in patients with advanced NSCLC. Patients with EGFR-mutant NSCLC displayed improved overall survival and PFS when treated with first-line EGFR-TKIs plus radiotherapy compared to TKI treatment alone.[21] Combined treatment of crizotinib and radiotherapy improved disease control and was associated with improved overall survival in patients with ALK-positive NSCLC.[19] The integration of TKIs with local therapies represents a promising novel treatment strategy in NSCLC with driver mutations.

This analysis is limited by its sample size and retrospective nature. A larger cohort is required to evaluate the impact of combining local therapy with brigatinib. Additionally, treatment modalities of local therapy vary in our study. In contrast to the BRIGHTSTAR study (NCT03707938), which investigates the impact of local consolidative therapy in combination with brigatinib, patients in our study received local therapy either prior or following brigatinib initiation. This variation in treatment timing in addition to the use of different treatment modalities (surgery, radiotherapy or both) introduce even more heterogeneity to our data. In contrast to the ALTA-1L study, where patients had an ECOG score between 0 and 2, all patients in our cohort had an ECOG score of 0. This could have contributed to a more favorable treatment outcome.

5. Conclusion

Despite the study's limitations, the outcomes suggest that a multidisciplinary therapy approach in patients with advanced or metastatic ALK-positive NSCLC with brigatinib combined with surgery and/or radiotherapy is safe and effective. Our data is consistent with safety profiles of the BRIGHTSTAR trial (NCT03707938) and studies examining efficacy of brigatinib in ALK-positive NSCLC patients.[4,10] The combination of both systemic and local therapy was well tolerated with the majority of AEs were low grade and manageable. Additionally, the promising ORR suggests that this combination treatment depicts an effective treatment regimen. Overall, our real-world data suggests safety and efficacy of brigatinib in combination with local therapy and contributes to the growing body of evidence in support of combining systemic targeted treatment local therapy.

Author contributions

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Data curation: Kristina Breitenecker, Anna Sophie Lang-Stöberl.

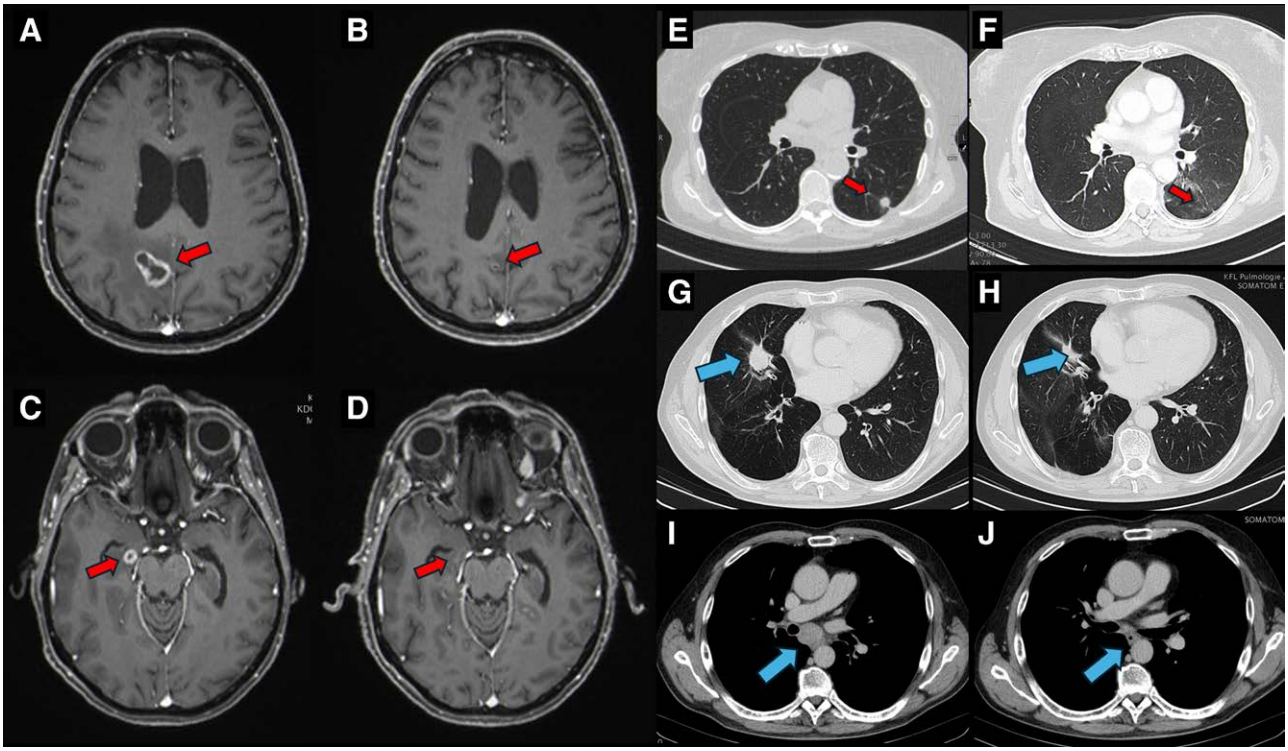

Figure 3. (A–F) Intracranial and systemic response (red arrows) in a 74-yr-old female patient. Contrast-enhanced T1-weighted images of the brain are shown. (G–J) Pre and posttreatment images of a 79-yr-old male with Stage IIIC adenocarcinoma, showing a PR to brigatinib in the primary tumor lesion in the right lung (G and H, blue arrows) and mediastinal lymph nodes (I and J, blue arrows). The patient subsequently underwent surgery and continued brigatinib as an adjuvant therapy. At the end of the study, the patient remained in remission. PR = partial response.

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References

[1] Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63.
[2] Politi K, Herbst RS. Lung cancer in the era of precision medicine. Clin Cancer Res. 2015;21:2213–20.
[3] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72:7–33.
[4] Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non–small-cell lung cancer. N Engl J Med. 2018;379:2027–39.
[5] Cognigni V, Pecci F, Lupi A, et al. The landscape of ALK-rearranged non-small cell lung cancer: a comprehensive review of clinicopathologic, genomic characteristics, and therapeutic perspectives. Cancers. 2022;14:4765.
[6] Solomon BJ, Mok T, Kim DW, et al; PROFILE 1014 Investigators. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371:2167–77.
[7] Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol. 2020;31:1056–64.
[8] Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK inhibitor–naive advanced ALK-positive NSCLC: final results of phase 3 ALTA-1L trial. J Thorac Oncol. 2021;16:2091–108.
[9] Solomon BJ, Liu G, Felip E, et al. Lorlatinib versus crizotinib in patients with advanced ALK-positive non–small cell lung cancer: 5-year outcomes from the phase III CROWN study. JCO. 2024;0:JCO.24.00581.
[10] Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase–positive non–small-cell lung cancer: a randomized, multicenter phase II trial. JCO. 2017;35:2490–8.
[11] Bivona TG, Doebele RC. A framework for understanding and targeting residual disease in oncogene-driven solid cancers. Nat Med. 2016;22:472–8.
[12] Elamin Y, Gandhi S, Saad M, et al. OA22.04 BRIGHTSTAR local consolidative therapy with brigatinib in tyrosine kinase inhibitor-naïve ALK-rearranged metastatic NSCLC. J Thorac Oncol. 2023;18:S96.
[13] World Medical Association. World Medical Association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310:2191–4.
[14] Travis WD, Brambilla E, Nicholson AG, et al; WHO Panel. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol. 2015;10:1243–60.
[15] Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. Chest. 2017;151:193–203.
[16] Organisation mondiale de la santé, Centre international de recherche sur le cancer, eds. Thoracic Tumours. 5th ed. International agency for research on cancer; 2021.

[17] Wu YL, Dziadziuszko R, Ahn JS, et al. Alectinib in resected ALK-positive non-small-cell lung cancer. N Engl J Med. 2024;390:1265–76.
[18] Wu YL, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med. 2020;383:1711–23.
[19] Gan GN, Weickhardt AJ, Scheier B, et al. Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. Int J Radiat Oncol Biol Phys. 2014;88:892–8.
[20] Elamin Y, Gandhi S, Antonoff M, et al. BRIGHTSTAR: a pilot trial of local consolidative therapy (LCT) with brigatinib in tyrosine kinase inhibitor (TKI)-naïve ALK-rearranged advanced NSCLC. JCO. 2020;38(15_suppl):9624–9624.
[21] Wang XS, Bai YF, Verma V, et al. Randomized trial of first-line tyrosine kinase inhibitor with or without radiotherapy for synchronous oligometastatic EGFR-mutated non-small cell lung cancer. J Natl Cancer Inst. 2023;115:742–8.
[22] Tsuboi M, Weder W, Escriu C, et al. Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for EGFR-mutated resectable non-small-cell lung cancer: NeoADAURA. Future Oncol. 2021;17:4045–55.